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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,884	07/15/2005	James Woods	JG-RMC-5139PCT/US 500954.	2685

26418 7590 10/10/2006

REED SMITH, LLP
ATTN: PATENT RECORDS DEPARTMENT
599 LEXINGTON AVENUE, 29TH FLOOR
NEW YORK, NY 10022-7650

EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,884	WOODS ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6-12 and 14* is/are allowed.

6)☒ Claim(s) *1-5, 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13, recites "further comprising using an antigen formed by covalently linking N-acetyl-3,5-dichlorotyprosine to a carrier protein. It is not clear whether or not the antigen and carrier protein is the same antigen and carrier protein as recited in claim 12, from which claim 13 depends, or whether it is in addition. It is also not clear whether or not the N-acetyl-3,5-dichlorotyprosine is a species of N-acetyl-3-chlorotyrosine as recited in claim 12, or whether N-acetyl-3,5-dichlorotyprosine is used in addition to the N-acetyl-3-chlorotyrosine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinecke, 6,096,556, in view of Bougueleret et al., 6,329,340, and further in view of Fischetti et al., 2002/0098234.

As to claim 1, Applicants claim a method for determining the presence of hypochlorous acid in vaginal secretions comprising measuring the presence and amount of 3-chlorotyrosine in the vaginal secretions.

Heinecke teaches that 3-chlorotyrosine are produced when reactive nitrogen or hypochlorous acid, respectively, oxidize proteins, but they do not appear when a wide variety of other oxidation systems are oxidizing agents (col. 9, lines 5-10.) Heinecke teaches that thus, determination of 3-nitrotyrosine and 3-chlorotyrosine in urine may provide sensitive and specific measures of oxidative damage by reactive nitrogen species or activated phagocytes in vivo (col. 9,lines 13-16). However, Heinecke does not teach measuring the presence and amount of 3-chlorotyrosine in vaginal secretions.

However Bougueleret et al. teach that antimicrobial substances are key elements in the defense of multicellular organisms and that among these substances are simple inorganic compounds, such as hypochlorous acid, and complex proteins and peptides (col. 1, lines 20-24). Bougueleret et al. teach that these are present at the first lines of defense, at the surface of mucous membranes of various organs (col. 1, lines 24-25).

Moreover, Fischetti et al. teach that vaginal infections can cause premature birth and subsequent complications in neonatal sepsis (page 2, paragraph 0024).

One of ordinary skill in the art would have been motivated to detect vaginal infections because Fishchetti et al. teach that vaginal infections can cause premature

birth. Moreover, it would have been obvious to one of ordinary skill in the art to detect for hypochlorous acid in vaginal secretions to detect vaginal infections because Bouguelert et al. teach that hypochlorous acid is an antimicrobial substance and is part of the first lines of defense at the surface of mucous membranes. Moreover, it would have been obvious to detect 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect hypochlorous acid because, as indicated above, Heinecke teaches that 3-chlorotyrosine are produced when reactive nitrogen or hypochlorous acid, respectively, oxidize proteins, but they do not appear when a wide variety of other oxidation systems are oxidizing agents (col. 9, lines 5-10), and that thus, determination of 3-nitrotyrosine and 3-chlorotyrosine in urine may provide sensitive and specific measures of oxidative damage by reactive nitrogen species or activated phagocytes in vivo (col. 9,lines 13-16). That is, given the disclosure of Heinecke, if 3-chlorotyrosine (as well as 3-nitrotyrosine) is detected, then it is a result of the presence of hypochlorous acid, and thus it would have been obvious that the presence and amount of 3-chlorotyrosine is directly related to the presence and amount of hypochlorous acid. Thus, it would have been obvious to detect the presence and amount of 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect the presence and amount of hypochlorous acid.

As to claim 2, Applicants claim a method for determining the likelihood of preterm premature rupture of fetal membranes or preterm labor in a pregnant female comprising the steps of: obtaining a sample of vaginal secretions from the female; and analyzing the sample for the presence and amount of hypochlorous acid by measuring the amount of 3-chlorotyrosine in the sample. As indicated in the discussion above regarding claim

1, one of ordinary skill in the art would have been motivated to detect vaginal infections because Fishchetti et al. teach that vaginal infections can cause premature birth (i.e., preterm labor). Moreover, it would have been obvious to one of ordinary skill in the art to detect for hypochlorous acid in vaginal secretions to detect vaginal infections because Bouguelert et al. teach that hypochlorous acid is an antimicrobial substance and is part of the first lines of defense at the surface of mucous membranes. Moreover, it would have been obvious to detect 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect hypochlorous acid because, as indicated above, Heinecke teaches that 3-chlorotyrosine are produced when reactive nitrogen or hypochlorous acid, respectively, oxidize proteins, but they do not appear when a wide variety of other oxidation systems are oxidizing agents (col. 9, lines 5-10), and that thus, determination of 3-nitrotyrosine and 3-chlorotyrosine in urine may provide sensitive and specific measures of oxidative damage by reactive nitrogen species or activated phagocytes in vivo (col. 9,lines 13-16). That is, given the disclosure of Heinecke, if 3-chlorotyrosine (as well as 3-nitrotyrosine) is detected, then it is a result of the presence of hypochlorous acid, and thus it would have been obvious that the presence and amount of 3-chlorotyrosine is directly related to the presence and amount of hypochlorous acid. Thus, it would have been obvious to detect the presence and amount of 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect the presence and amount of hypochlorous acid.

As to claim 3, Applicants claim a method for therapeutically treating a pregnant female to minimize the likelihood of preterm premature rupture of fetal membranes or preterm labor comprising the steps of: obtaining a sample of vaginal secretion from the

female; measuring the presence and amount of 3-chlorotyrosine in the vaginal secretions wherein an increased amount of 3-chlorotyrosine represents an increased likelihood of preterm premature rupture of fetal membranes or preterm labor; and administering an amount of dietary antioxidant to the female if the likelihood is increased. The method of detecting the presence and amount of 3-chlorotyrosine to detect preterm labor (i.e., premature birth) would have been obvious over Heinecke in view of Bougueleret et al., 6,329,340 and Fischetti et al., as discussed above regarding claim 2. However, these references do not teach therapeutically treating a pregnant female by administering an amount of dietary antioxidant if the likelihood of preterm labor is increased. However, Heinecke teaches that in vivo oxidative damage is reduced by vitamin E supplements (col. 8, line 64 – col. 9, line 1). Heinecke also teaches that 3-chlorotyrosine oxidizes proteins (col. 9, lines 7-10). Thus, it would have been obvious to one of ordinary skill in the art that administration of dietary vitamin E (an antioxidant) will reduce oxidative damage caused by hypochlorous acid, which is taught by Heinecke to be an oxidizing agent. Thus, it would have been obvious to one of ordinary skill in the art to administer dietary vitamin E if it is found that there is vaginal infection (from the presence of hypochlorous acid, as determined by the detection of 3-chlorotyrosine, as explained above), in order to reduce oxidative damage, as would be desirable to reduce the likelihood of preterm labor, given the teachings of Fischetti et al. that vaginal infections can cause premature birth.

As to claim 4, the dietary antioxidant is vitamin E (see Heinecke, col. 8, line 64 – col. 9, line 1).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heinecke, 6,096,556, in view of Bougueleret et al., 6,329,340, and further in view of Fischetti et al., 2002/0098234, and Heinecke, 6,268,220.

Applicants claim a method for determining the presence of hypochlorous acid in female vaginal secretions comprising measuring the presence and amount of 3-chlorotyrosine in the vaginal fluid using an ELISA assay.

Heinecke teaches that 3-chlorotyrosine are produced when reactive nitrogen or hypochlorous acid, respectively, oxidize proteins, but they do not appear when a wide variety of other oxidation systems are oxidizing agents (col. 9, lines 5-10.) Heinecke teaches that thus, determination of 3-nitrotyrosine and 3-chlorotyrosine in urine may provide sensitive and specific measures of oxidative damage by reactive nitrogen species or activated phagocytes in vivo (col. 9,lines 13-16). However, Heinecke does not teach measuring the presence and amount of 3-chlorotyrosine in vaginal secretions.

However Bougueleret et al. teach that antimicrobial substances are key elements in the defense of multicellular organisms and that among these substances are simple inorganic compounds, such as hypochlorous acid, and complex proteins and peptides (col. 1, lines 20-24). Bougueleret et al. teach that these are present at the first lines of defense, at the surface of mucous membranes of various organs (col. 1, lines 24-25).

Moreover, Fischetti et al. teach that vaginal infections can cause premature birth and subsequent complications in neonatal sepsis (page 2, paragraph 0024).

One of ordinary skill in the art would have been motivated to detect vaginal infections because Fishchetti et al. teach that vaginal infections can cause premature birth. Moreover, it would have been obvious to one of ordinary skill in the art to detect for hypochlorous acid in vaginal secretions to detect vaginal infections because Bouguelert et al. teach that hypochlorous acid is an antimicrobial substance and is part of the first lines of defense at the surface of mucous membranes. Moreover, it would have been obvious to detect 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect hypochlorous acid because, as indicated above, Heinecke teaches that 3-chlorotyrosine are produced when reactive nitrogen or hypochlorous acid, respectively, oxidize proteins, but they do not appear when a wide variety of other oxidation systems are oxidizing agents (col. 9, lines 5-10), and that thus, determination of 3-nitrotyrosine and 3-chlorotyrosine in urine may provide sensitive and specific measures of oxidative damage by reactive nitrogen species or activated phagocytes in vivo (col. 9,lines 13-16). That is, given the disclosure of Heinecke, if 3-chlorotyrosine (as well as 3-nitrotyrosine) is detected, then it is a result of the presence of hypochlorous acid, and thus it would have been obvious that the presence and amount of 3-chlorotyrosine is directly related to the presence and amount of hypochlorous acid. Thus, it would have been obvious to detect the presence and amount of 3-chlorotyrosine (in addition to 3-nitrotyrosine) to detect the presence and amount of hypochlorous acid.

However, neither Heinecke in patent number 6,096,556, nor Bougueleret et al., nor Fischetti et al. teach that the measuring for the presence and amount of 3-chlorotyrosine is performed using an ELISA assay.

However, Heinecke in patent number 6,268,220 teaches that the presence and level of 3-chlorotyrosine is determined by an immunoassay with antibodies to the 3-chlorotyrosine, including ELISA (col. 9, lines 8-16). It would have been obvious to one of ordinary skill in the art to utilize an ELISA to determine the presence and amount of 3-chlorotyrosine in the method discussed above because Heinecke in patent number 6,268,220 teaches that an ELISA using antibodies is a known method of detecting 3-chlorotyrosine, and one of ordinary skill in the art would utilize this known ELISA method as it would allow for the detection of the analyte of interest, in this case 3-chlorotyrosine.

Allowable Subject Matter

Claims 6-12 and 14 are allowed.

Claim 13 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter for claims 6-11: 3-(3-chloro-4-hydroxy-benzyl)-6-mercaptomethyl-piperazine-2,5, dione was not found in the prior art.

The following is a statement of reasons for the indication of allowable subject matter for claims 12-14: a method for raising antibodies to 3-chlorotyrosine using an antigen formed by covalently linking N-acetyl-3-chlorotyrosine, or N-acetyl-3,5-dichlorotyprosine to a carrier protein was not found in the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ann Lam 10/4/06